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Cobalt-Catalyzed Hydroazidation of Olefins: Convenient Access to Alkyl Azides

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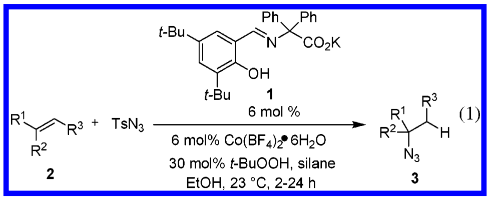
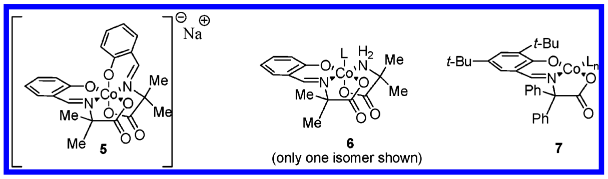
Amines and related functional groups are ubiquitous in natural products as well as pharmaceutical substances. Consequently, the development of methods for the introduction of nitrogen in simple organic compounds is an intense focus of research.[1] Azides are easily converted into either amines[2a] or pharmaceutically relevant heterocycles.[2b,c] Furthermore, they have recently generated much interest due to their stability under physiological conditions and their unique reactivity, which permits their use in bioconjugation via Staudinger ligation[2d] or click chemistry.[2e] The most common access route to alkyl azides involves the substitution reaction of primary or secondary alkyl halides with inorganic azides.[3] The direct reaction of alkenes with hydrazoic acid sources is limited to alkenes that give rise to stabilized carbocations and require excess HN_3,[4a] $TMSN_3$,[4b] or zeolite-supported NaN_3,[4c] unactivated monosubstituted olefins being described as unreactive in these processes.[4] Herein we report the functionalization reaction of unactivated olefins to the corresponding azides with high Markovnikov selectivity using tosyl azide (TsN_3) and a silane. The reaction is mediated by a simple cobalt catalyst prepared in situ from Schiff base **1** and $Co(BF_4)_2 \cdot 6H_2O$ (eq 1).



We have recently documented the Co- and Mn-catalyzed hydrohydrazination reaction of alkenes ($RO_2CN{=}NCO_2R$ + alkene → *N*-alkyl hydrazine).[5] This reaction is the nitrogen equivalent of the olefin hydration reaction developed by Mukaiyama and Isayama[6a] and displays broad substrate scope. In our ongoing search for other nitrogen sources that would be amenable for use in olefin functionalization processes, we have examined sulfonyl azides, as they are convenient, readily available, and widely handled reagents in the laboratory.[7] Moreover, we speculated that sulfonyl azides could display parallel reactivity to that observed with azodicarboxylates in the cobalt- and manganese-mediated processes.

Given our prior success with $Mn(dpm)_3$[8] and cobalt complexes in the hydrohydrazination reaction, we first examined their use together with 1.6 equiv of phenylsilane and 3 equiv of ethyl sulfonyl azide for the hydroazidation of 4-phenylbutene (**4**) as a test substrate. The manganese complex failed to provide azide product, and the cobalt complex obtained from $Co(NO_3) \cdot 6H_2O$, 2-aminoisobutyric acid, salicylaldehyde, NaOH, and H_2O_2 in ethanol[9] afforded 4-phenyl-2-azidobutane in 50% yield after 48 h. Further extensive optimization of the reaction conditions did not lead to any improvements. Knowing that the catalyst used still contains impurities, we re-examined the preparation of the complex, with the hope that greater purity would result in increased reactivity. Using $Co(OH)_3$ as catalyst precursor,[9] we succeeded in isolating complex **5** (Chart 1), which we thought to be the active catalyst for the hydrohydrazination reaction; however, this complex was inactive in olefin hydroazidation. Analysis of the mass spectrum revealed complex **6** to be present in the mixture obtained via the in situ oxidation procedure en route to **5**. Complex **6** could be prepared by refluxing a 1:1:1 mixture of salicylaldehyde, 2-aminoisobutyric acid, and $Co(OAc)_2 \cdot 4H_2O$ in water under argon, collecting the precipitating solid and oxidizing it in air in the presence of 1 equiv of 2-amino-isobutyric acid in ethanol. The activity of the complex obtained was comparable to that observed with the mixture isolated using our original protocol.

Chart 1



The identification of a cobalt complex incorporating a single tridentate ligand in the active catalyst presented new opportunities for catalyst design. We speculated that increasing the steric bulk around the tridentate ligand could lead to a complex with enhanced stability and perhaps greater activity. With this design strategy in mind, **7** was synthesized. Preformation of Schiff base **1** derived from 3,5-di-*tert*-butyl salicylaldehyde and α,α-diphenyl glycine followed by reaction with $Co(NO_3)_2 \cdot 6H_2O$ and oxidation with H_2O_2 proved crucial to the isolation of **7**. Interestingly, coordination of a second molecule of α,α-diphenyl glycine to the cobalt center was never observed by NMR and mass spectroscopy. Nonetheless, we observed that **7** was indeed a better catalyst, converting 4-phenylbutene (**4**) to the desired azide in 12 h in 60% yield. Further investigations revealed a batch-to-batch dependency with some catalyst preparations showing lower reactivity and long (up to 12 h) initiation period. Inspired by Mukaiyama's work in olefin hydration,[6] we used 30% *t*-BuOOH as an additive to facilitate initiation of the reaction. We were gratified to observe full conversion to product in 2−8 h under otherwise identical conditions. In the optimal procedure, in situ preparation of the catalyst from $Co(BF_4)_2 \cdot 6H_2O$ and **1** gave 70% of the desired azide in 1.5 h, allowing reproducible yields and reaction times.

Analysis of the reaction mixture led to the identification of 4-phenylbutane as the major side product (28% yield). At this point, we decided to vary the structure of both silane and sulfonyl azide, hoping to increase the ratio of products in favor of the alkyl azide. Tosyl azide proved to be best, increasing the azide/alkane ratio from 3:1 to 9:1 (as determined by GC). Finally, using tetramethyldisiloxane (TMDSO) and tosyl azide, we found that the ratio was increased to 20:1, albeit with slight attenuation of reactivity (reaction time 3 h instead of 2 h). Using the optimized procedure, we routinely obtained 4-phenyl-2-azido-butane in 85−90% yield.

With a reliable procedure in hand, we proceed to examine the scope of the hydroazidation reaction, with both phenylsilane and

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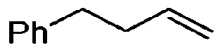
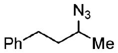
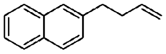
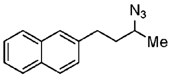
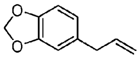
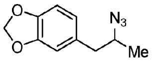
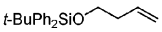
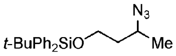
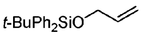
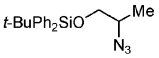
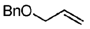
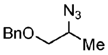
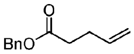
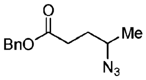
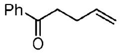
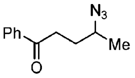
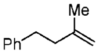
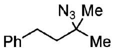
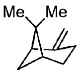
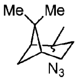
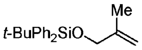
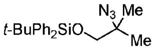
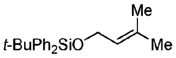
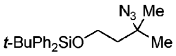
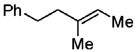
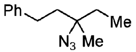
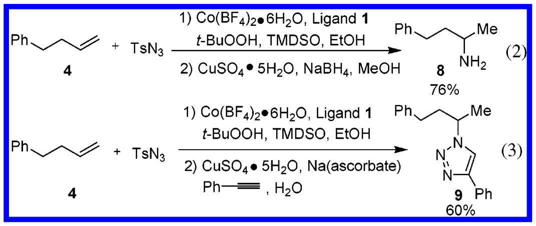
Table 1. Hydroazidation Reaction of Olefins (Eq 1)

Entry	Alkene	Product	Yield[a)] with $PhSiH_3$	Yield[b)] with TMDSO
1			90%	86%
2			72%	69%
3			65%	62%
4			73%	85%[c)]
5			55%	67%
6			35%	39%[c)]
7			75%	77%
8			49%[d)]	46%[d)]
9			86%	90%
10			89% dr: 4:1	76%[c)] dr: 4:1
11			73%[d)]	58%[c),d)]
12			63%[d)]	48%[c),d)]
13			66%	48%[c),d)]

[a] General procedure **A**: 0.5 mmol alkene, 0.8 mmol $PhSiH_3$, 1.5 mmol TsN_3, 30 mol % *t*-BuOOH, 6 mol % ligand **1**, 6 mol % $Co(BF_4)_2{\cdot}6H_2O$, 2.5 mL of ethanol at 23 °C under argon. [b] General procedure **B**: 1.0 mmol TMDSO was used instead of $PhSiH_3$. [c] 2.0 mmol TMDSO were used. [d] Starting material was partially recovered (see Supporting Information for further details).

TMDSO (Table 1). All the terminal olefins tested (entries 1−8) showed excellent Markovnikov selectivity. TMDSO is generally better for this class of olefins as less alkane side products are formed; when this observation is coupled with the fact that it is also inexpensive, it is rendered the more convenient reagent for the reaction. An aromatic ring in allylic or homoallylic position was well-tolerated (entries 1−3), but styrene derivatives (not shown) were not active, although they had proven to be excellent substrates for the related hydrohydrazination reaction. Homoallylic and allylic ethers were also good substrates (entries 4−6), provided a bulky silyl protecting group was used. The free alcohols proved to be inactive. Esters and ketones were tolerated (entries 7 and 8). Chemoselectivity was excellent, as no reduction of the ketone was observed. Geminally disubstituted and trisubstituted olefins were also good substrates for this reaction, furnishing the tertiary azide exclusively (entries 9−13). For these substrates, phenylsilane proved to be the reductant of choice, due to its higher reactivity.

The mild conditions of the olefin hydroazidation reaction permitted us to examine various processes that effect the conversion of the product to other useful compounds without the need of isolation and purification of the azides themselves. We have observed that the one-pot conversions of olefins to amines using in situ reduction[2a] (eq 2) and to 1,4-disubstituted triazoles using Sharpless' procedure[2b] (eq 3) were feasible in useful yields for 4-phenylbutene (**4**) as the prototypical substrate. In the reduction reaction, a simple extraction procedure sufficed to allow isolation of the free amine in 76% yield and 95% purity, as determined by NMR.



We have documented the cobalt-catalyzed hydroazidation reaction as a new entry to alkyl azides directly from unactivated olefins. The method complements existing approaches based on substitution of alkyl halides or hydrazoic acid addition to activated olefins. In addition to the azides that can be generated, the reaction can be coupled to processes such as reduction to give rise to amines and cycloaddition giving useful heterocycles. Further studies are being conducted to better understand the similarities and differences between this process and the hydrohydrazination reaction, with the aim of discovering more efficient and versatile catalytic systems.

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Supporting Information Available: Experimental procedures and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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